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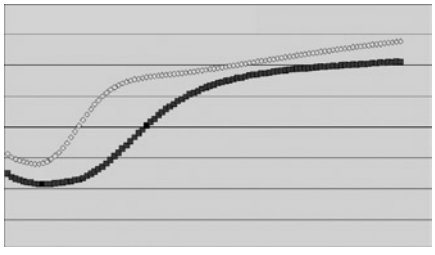
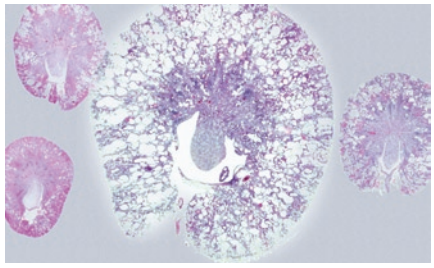
Dose–response curve of epoetin in dialysis patients

Most patients on hemodialysis receive erythropoietin (epoetin) to treat anemia, yet the dose–response curve for the treatment has not been examined in a detailed manner. It is not practical to study large numbers of patients on hemodialysis to provide a rigorous pharmacological study. Hence, many previous studies have relied on administrative databases. Also, many clinicians give patients with the lowest hematocrits (of whatever cause) the largest amount of epoetin. This confounding factor was eliminated in a study reported in this issue. Cotter *et al.* used a 'marginal structural' model adjusting for the time-dependent influence of the indication for treatment. Using the United States Renal Data System to monitor older patients who started dialysis and epoetin treatment, the authors found that the hematocrit response to average weekly epoetin doses showed an S-shaped dose–response relationship. The dose required to maintain a given hematocrit was lower than that to induce the same change at initiation of therapy. The dose–response curve found in this study suggests that published recommendations for a starting dose of epoetin are appropriate; a starting dose of 7,500–15,000 units per week can maintain the hematocrit level in the desired target range of 33%–36%. **See page 347.**



Calcium channel inhibition and PKD

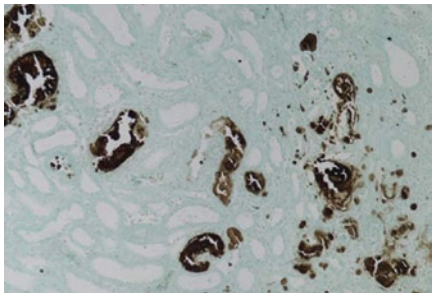
Cells lining the cysts of polycystic kidney disease (PKD) are less differentiated and proliferate more than normal, terminally differentiated tubular epithelial cells. Cyclic



adenosine monophosphate (cAMP) seems to be the culprit in this process. This second messenger is antiproliferative in normal epithelial cells, but it increases the proliferation of the mutant cells. Low cell calcium seems to be involved in this process as well, since blockade of calcium channels into normal cells causes cAMP-dependent mitogenesis. Much of this information was developed *in vitro* with the use of cells taken from human or mouse models of PKD. Nagao *et al.* studied the mechanism *in vivo* in the Cy/+ PKD rat, a model of the dominant variety of PKD, before and after treatment with the calcium channel blocker verapamil. Treatment increased kidney weight and enlarged cysts, which was associated with more cell proliferation and apoptosis, and increased signaling through the mitogen-activated protein kinases. Verapamil had no effect on kidney morphology in wild-type rats. These findings show that calcium channel blockers accelerate cyst growth in the presence of endogenous cAMP, thus exacerbating PKD. **See page 269.**

Calcimimetics and vascular calcification

Soft-tissue calcification is emerging as a serious consequence of hyperparathyroidism seen in renal failure. In a new study, Lopez *et al.* show the effect of treating uremic rats with vitamin D derivatives (calcitriol or paricalcitol) or with blockers of the calcium-sensing receptor (calcimimetics). A new calcimimetic, AMG 641, was used alone or in combination with vitamin D derivatives. After the induction of renal failure, all animals developed secondary hyperparathyroidism. Treatment with the calcimimetic or vitamin D analogues reduced parathyroid hormone levels as expected, but treatment with a combination of calcimimetic and paricalcitol was most effective. Vitamin D analogue treatment increased aortic calcification, whereas calcimimetic treatment did not lead to extraskeletal calcification. Vitamin D analogue treatment resulted in a higher mortality, which was blunted by coadministration of the calcium receptor blocker. When used in combination with paricalcitol, AMG 641 provided excellent control of secondary hyperparathyroidism and prevented mortality associated with the use of vitamin D derivatives without causing tissue calcification. **See page 300.**



Heparanase and anionic sites

Fixed negative charges in the glomerular basement membranes are a classic deterrent to the passage of albumin across the filtration barrier. It has been shown that many of these fixed charges are due to heparan sulfate proteoglycans. Further, in a number of diseases associated with proteinuria, there is increased expression of heparanase in the glomerulus. Since it is an enzyme, heparanase is expected to reduce the negative charges by degrading the heparan sulfate proteoglycans. In a new study, mice that transgenically overexpress heparanase were examined. Remarkably, no change occurred in the morphology or function in these animals, especially proteinuria. Yet the majority of the glycosaminoglycans were removed. Although some heparanase-resistant anionic sites may exist, the study does demonstrate the complexity of measuring these anionic sites. An excellent Commentary by Morita *et al.* addresses the methodological issues of measuring anionic sites. **See page 247.**